Claims

1. (original) A kit of reagents for nucleic acid amplification comprising:

a single-stranded external control polynucleotide, a forward primer, a reverse primer, a polymerase, a detectable probe, and one or more nucleotide 5'-triphosphates;

wherein the forward primer and the detectable probe are separated by 0 to 5 nucleotides when hybridized to the external control polynucleotide, or its complement, and the reverse primer and the detectable probe are separated by 0 to 5 nucleotides when hybridized to the external control polynucleotide, or its complement.

2. (original) The kit of claim 1 wherein the forward primer and reverse primer are each 10 to 40 nucleotides in length.

3. (original) The kit of claim 1 wherein the single-stranded external control polynucleotide is 30 to 110 nucleotides in length.

4. (original) The kit of claim 1 wherein the single-stranded external control polynucleotide is 50 to 70 nucleotides in length.

5. (original) The kit of claim 1 wherein the external control polynucleotide, or its complement, forms single-stranded overhangs consisting of 1 to about 10 nucleotides when hybridized to the forward primer or to the reverse primer.

6. (original) The kit of claim 1 wherein said polymerase is a thermostable polymerase with 5' nuclease activity.

7. (original) The kit of claim 1 wherein the detectable probe comprises a fluorescent dye.

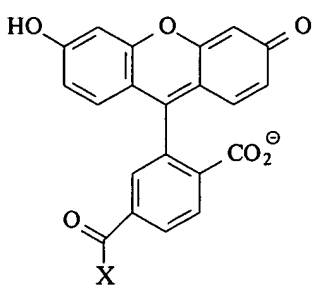
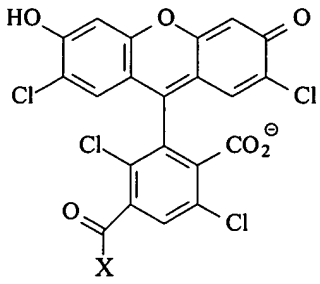
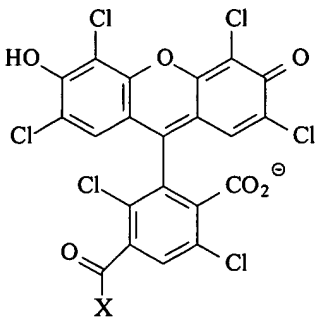
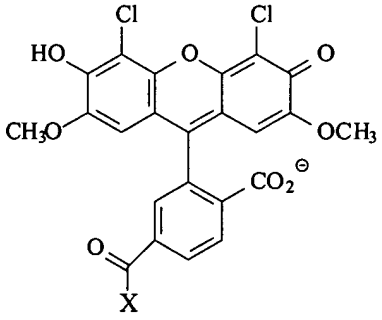
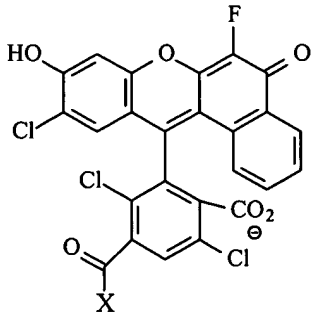
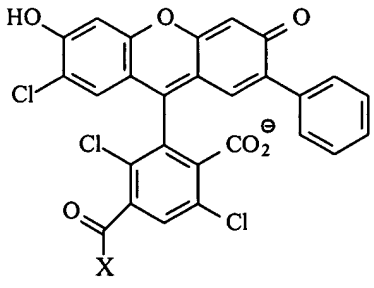
8. (original) The kit of claim 1 wherein the detectable probe is a self-quenching fluorescence probe comprising a reporter dye and a quencher.

9. (original) The kit of claim 8 wherein the self-quenching fluorescence probe is 10 to 40 nucleotides in length.

10. (original) The kit of claim 8 wherein said reporter dye is a xanthene dye.

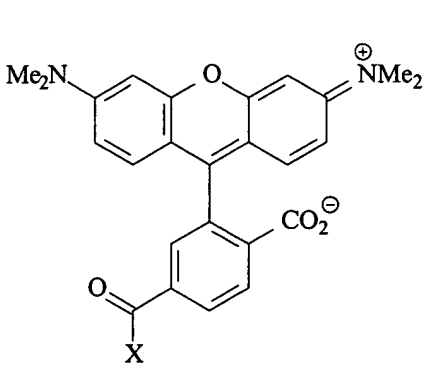
11. (original) The kit of claim 10 wherein said xanthene dye is a fluorescein dye.

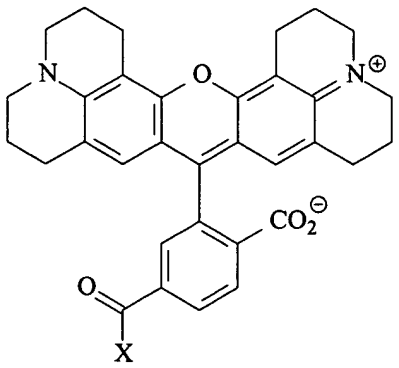
12. (original) The kit of claim 11 wherein said fluorescein dye is selected from the group consisting of:

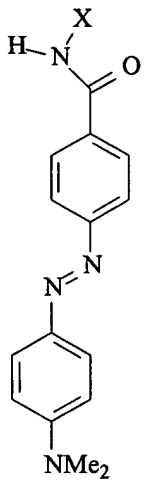







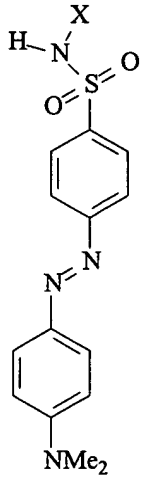
where X is an attachment site to the probe.

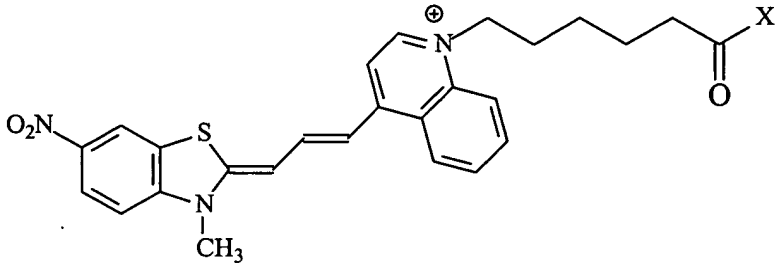
13. (original) The kit of claim 8 wherein said quencher is selected from the group consisting of:











where X is an attachment site to the probe.

14. (original) The kit of claim 8 wherein said reporter dye is separated from said quencher by at least 12 nucleotides.

15. (original) The kit of claim 8 wherein said reporter dye is attached at a 5' terminus or a 3' terminus of the self-quenching fluorescence probe.

16. (original) The kit of claim 8 wherein said quencher is attached at a 5' terminus or a 3' terminus of the self-quenching fluorescence probe.

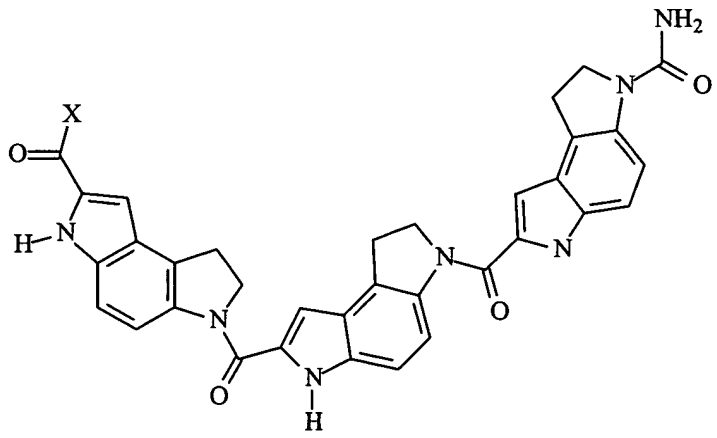
17. (original) The kit of claim 8 wherein said quencher is non-fluorescent.

18. (original) The kit of claim 1 wherein the detectable probe is labelled with a minor groove binder.

19. (original) The kit of claim 8 wherein the self-quenching fluorescence probe is labelled with a minor groove binder.

20. (original) The kit of claim 8 wherein the self-quenching fluorescence probe is labelled with a minor groove binder at a 3' terminus nucleotide.

21. (original) The kit of claim 19 wherein the minor groove binder has the structure:



where X is an attachment site to the probe.

22. (original) The kit of claim 1 where one or more nucleotide 5'-triphosphates comprises a fluorescent dye, a quencher, biotin, or a minor groove binder.

23. (original) The kit of claim 8 further comprising a second self-quenching fluorescence probe comprising a reporter dye and a quencher wherein the sequences of the first self-quenching fluorescence probe and second self-quenching fluorescence probe differ by a single nucleotide.

24. (original) The kit of claim 1 wherein the concentration of the forward primer and the concentration of the reverse primer is each about 10 to 100 μM, the concentration of each nucleotide 5'-triphosphate is about 100 to 1000 μM, and the concentration of the self-quenching fluorescence probe is about 1 to 100 μM.

25. (original) The kit of claim 1 further comprising a second single-stranded external control polynucleotide wherein the forward primer and the detectable probe are separated by 0 to 5 nucleotides when hybridized to the second external control polynucleotide, or its complement, and the reverse primer and the detectable probe are separated by 0 to 5 nucleotides when hybridized to the external control polynucleotide, or its complement; and

wherein the sequence complementary to the detectable probe of the first single-stranded external control polynucleotide differs from the sequence complementary to the detectable probe of the second single-stranded external control polynucleotide by one or more nucleotides, nucleotide insertions, or nucleotide deletions.

26. (previously presented) The kit of claim 1 where the reagents are delivered by robotic means to one or more vessels.

27. (original) The kit of claim 26 where the reagents are spotted on an absorbent or porous material.

28. (original) The kit of claim 26 where the reagents are spotted on a non-absorbent and planar surface.

29. (original) The kit of claim 26 wherein the reagents are located in an array configuration having 6 to 1536 reaction sites.

30. (original) The kit of claim 29 wherein the reagents are located in a microwell tray having 96 to 384 wells.

31. (original) The kit of claim 30 wherein each well has a volume from 1 to 500 μl.

1. Rejection under 35USC§102(e) or in the alternative under 103(a)

102(e) Analysis

The Examiner rejected claims 1-16, 23, and 26-31 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Aoyagi et al. (5,952,202). The rejection is respectfully traversed.

In a previous response sent on May 6, 2003, applicants pointed out that their claimed invention, unlike Aoyagi, teaches the following element of claim 1 of the instant application, "wherein the forward primer and the detectable probe are separated by 0 to 5 nucleotides when hybridized to the external control polynucleotide, or its complement, and the reverse primer and the detectable probe are separated by 0 to 5 nucleotides when hybridized to the external control polynucleotide, or its complement." Applicants' argued on May 6, 2003, that since Aoyagi fails to teach this limitation, Aoyagi is not an appropriate 102(e) reference, nor is it an appropriate 103(a) reference.

In the Examiner's response to the May 6, 2003 response, the Examiner argued that the language "external control" is intended use, and is equivalent to the external control polynucleotide of applicants' claimed invention, "since they both are polynucleotide used as control polynucleotide in polymerase chain reaction."

Applicants' respectfully disagreed in a response filed January 29, 2004, and argued that the language "external control" is not intended use. "External control" is an element and limitation of the claimed invention. It is a characteristic of the claimed invention that the external control is in a separate reaction. As Examiner notes "Aoyagi et al., do not disclose the kit which comprises an external control polynucleotide." Since Aoyagi fails to teach this element, Aoyagi is not an appropriate 102(e) reference. Applicants then respectfully requested reconsideration. While applicants could reiterate these arguments, these arguments are now believed moot in light of 103(c), which applicants assert applies to applicant's claimed invention in light of the Aoyagi reference. 103(c) states:

"Subject matter developed by another person, which qualifies as prior art only under one or more of subjections (e), (f), and (g) of section 102 of this title, shall not preclude patentability

under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

Evidentiary support that applicants were under an obligation to assign their invention to the same assignee as Aoyagi will be forthcoming in a subsequent correspondence.

1. Rejection under 35USC§102(e) or in the alternative under 103(a)

103(a) Analysis

The Examiner rejected claims 1-16, 23 and 26-31 under 103(a) over Aoyagi, stating "One of ordinary skill in the art would have been motivated to construct the kit comprising an external control polynucleotide as claimed because as addressed by Aoyagi et al., kits make the practice of a method more reproducible and easier to perform." In a previous response sent on May 6, 2003, applicants pointed out as a first matter that not all controls are the same. The applicants' claimed invention comprises an *external* control polynucleotide. Such a control provides different information than the internal control taught in Aoyagi. The Examiner provided no basis for showing that one having ordinary skill in the art would be motivated to remove the internal control polynucleotide taught by Aoyagi and place it in a different reaction. In the absence of establishing this motivation, the Examiner has not met the burden of establishing a prima facie case for obviousness. Thus, applicants' maintained that Aoyagi is not an appropriate 103(a) reference, and reconsideration was respectfully requested. While Applicants could reiterate this argument here, applicants assert that 103(a) arguments are moot in light of the obligation of the inventors, at the time of invention, to assign the invention to the same assignee as Aoyagi, and cite U.S.C. 103(c), which states:

"Subject matter developed by another person, which qualifies as prior art only under one or more of subjections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

2. Rejection under 35USC§103(a)

The Examiner rejects claims 24-25 under 103(a) over Aoyagi in the response dated July 29, 2003, stating *inter alia* that "it would have been prima facie obvious for one of ordinary skill in the art to include one more control polynucleotide in the kit for easier performing the method." The Examiner reiterated this rejection in the response dated March 4, 2004. Applicants believe this rejection is now moot in light of 103(c) as discussed supra.

3. Rejection under 35USC§103(a)

Examiner rejected claims 18-21 under 103(a) over Aoyagi as applied to claims 1-16, 23, and 26-31 above, and further in view of Kutyavin et al. (5,801,155), stating *inter alia* that "it would have been prima facie obvious for one of ordinary skill in the art to construct a kit including a minor groove binding molecules as claimed." The rejection was respectfully traversed with arguments in applicant's January 29th response. Applicants believe this rejection is now moot in light of 103(c) as discussed supra.

4. Rejection under 35USC§103(a)

Examiner rejected claim 17 under 103(a) over Aoyagi as applied to claims 1-16, 23, and 26-31 above, and further in view of Livak et al. (5,538,848) stating *inter alia* that "it would have been prima facie obvious for one of ordinary skill in the art to construct a kit including a quencher which is non-fluorescence as needed as claimed." The rejection was respectfully traversed with arguments in applicant's January 29th response. Applicants believe this rejection is now moot in light of 103(c) as discussed supra.

5. Rejection under 35USC§103(a)

Examiner rejected claim 22 under 103(a) over Aoyagi as applied to claims 1-16, 23, and 26-31 above, and further in view of Williams et al. (6,232,075) stating *inter alia* that "it would have been prima facie obvious for one of ordinary skill in the art at the time of the instant invention to include the nucleotide 5'-triphosphates comprising a fluorescent dye in the kit as

claimed." The rejection was respectfully traversed with arguments in applicant's January 29th response. Applicants believe this rejection is moot in light of 103(c) as discussed supra.

6. Applicants believe the above remarks and evidentiary support (to be provided in a subsequent correspondence) place the application in condition for allowance, and look forward to allowance of the claims as written.

FEE AUTHORIZATION and REQUEST FOR TIME EXTENSION

A Petition for a 5-Month Extension of Time is enclosed herewith. If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from Applied Biosystems Deposit Account No. **01-2213 (Order No. 4498C1)**.

Respectfully submitted,

Date: 8-30-04

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